REMARKS

The Examiner is thanked for the courtesies extended during the interview on March 30, 2001.

Claims 1, 12, 21 and 42-44 have been amended. Claims 10, 36, 37, 40 and 41 have been canceled. After entry of these amendments, claims 1-9, 11-35, 38, 39, and 42-44 will be pending in the instant application.

Election/Restriction Requirement

Applicants confirm the election of Group I, including claims 1-35, 38, 39, and 42-44, as provisionally elected on October 26, 2000. Applicants reserve the right to pursue prosecution of the non-elected claims in another application.

Claim Rejection Under 35 U.S.C.§101.

Claims 42-44 are rejected under 35 U.S.C. §101 as drawn to non-statutory subject matter.

Claims 42-44 have been amended to recite "isolated" progenitors, as suggested by the Examiner to clarify that the claims are not meant to read on a product of nature. Reconsideration is respectfully requested.

Claim Rejection Under 35 U.S.C. §112.

Claims 27-35 and 39 were rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not enabled by the disclosure. Applicants respectfully disagree.

In the instant application, Applicants provide an extensive disclosure of treatment of liver dysfunction or disease in support of claims 27-35 and 39 at a level of detail and precision current in the art. In a case where antibody affinities were used to define the invention, the Federal Circuit has stated that the level of precision need only be as precise as the art can offer. Hybritech v. Monoclonal Antibodies, Inc., 802 F. 2d 1367 (Fed. Cir. 1986). Applicants respectfully draw the Examiner's attention to the present specification, page 15 line 23 *et seq.*, page 16 line 3 *et seq.*, page 16 line 26 *et seq.*, page 22 line 16 *et seq.*, page 13 line 22 *et seq.* and

page 42 line 17 *et seq.* which teach the use of the isolated progenitors of the invention, and their progeny, for the treatment of liver diseases and dysfunctions. Applicants respectfully maintain that administration of suspensions of hepatocytes to subjects is not, of itself, a complicated procedure but, rather is known in the art and practiced by physicians. Moreover, Applicants provide suitable cell numbers for use in therapy, discuss the advantages of small cell size for minimizing embolus formation, and describe the advantages of hepatic progenitors vis-a-vis hepatocytes as resistant to immunological rejection. In addition, Applicants have found that hepatic progenitors have many advantages for use in cell therapy compared to hepatocytes, not the least of which is their proliferative capacity. Once the hepatic progenitors are administered they then go about the business of alleviating the medical condition affecting the liver.

The Examiner states that the specification is not enabled for the instant claims because it fails to provide sufficient teachings and guidance demonstrating that by administering human liver progenitors of the present application into a subject having liver dysfunction or disease, the subject would be treated for symptoms associated with the liver dysfunction or disease, and that there is a lack of nexus between a specific example and the methods of treatment.

The reference by Habibullah cited in the Information Disclosure Statement filed on even date herewith, reports the use of hepatocytes for treatment of fulminant liver failure by simple injection into the peritoneum. The treatment was successful for half of the hepatocyte-treated patients, whereas a greater proportion of control patients succumbed. Applicants assert that while treatment with hepatocytes is not the same as treatment with liver progenitors, the reference does establish the general validity and ease of cell therapy with liver-derived cells.

The Examiner rejected claim 35 because the disclosure of gene transfer with urokinase plasminogen activator "cannot be extrapolated to the instant claimed invention."

In the instant application, Applicants have provided details of providing hepatic precursors with an exogenous gene of interest and have provided a specific example of genetic modification of hepatic precursors with the urokinase gene, including the consequences of the transfection. The Applicants respectfully draw the Examiner's attention to support in the specification directed to human hepatic progenitors, their progeny, or more mature forms that harbor exogenous nucleic acid, including: page 14 line 11, page 22 line 22, page 23 line 1, page

42 line 3 *et seq.*, page 42 line 13, page 42 line 17 *et seq.*, page 42 line 26 *et seq.*, and Example 10 directed to use of the urokinase gene. It is not necessary to give an example of every such species. In fact, "[i]t is manifestly impracticable for an applicant who discloses a generic invention to give an example of every such species. It is sufficient if the disclosure teaches those skilled in the art what the invention is and how to practice it." In re Kamal, 398 F.2d 867 (C.C.P.A. 1968), quoting In re Grimme, 274 F.2d 949, 124 (C.C.P.A. 1960).

In addition, the specification describes the use of the cells of the invention as part of a composition for use in cell therapy, for example, on page 12 line 2 *et seq.*, and page 16 line 26 *et seq.*, including the use of a pharmaceutically acceptable carrier.

The Examiner rejects claim 39. Claim 39 claims a pharmaceutical composition comprising the composition of claim 21. No reason for the rejection of claim 39 is given, Applicants respectfully request clarification for the basis of the rejection of claim 39 and in the absence thereof, assert that claim 39 claims patentable subject matter and is allowable.

Claim Rejection Under 35 U.S.C. §112, second paragraph.

Claims 1-26, 38, 39, and 42 were rejected as being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. Applicants traverse this rejection.

The Examiner objected to the use of the words "substantially," "relatively large size," and "relatively small size" in claim 1.

Although Applicants consider that the terms used are well-understood in the art and unambiguously in view of the specification, claim 1 has been amended solely to facilitate prosecution. Hence, the phrase "substantially single" has been removed as suggested by the Examiner.

The meaning of "relatively large size" and "relatively small size" is well established in the disclosure of the invention and will be clear to one skilled in the art upon examination of the specification. For example, the specification teaches that: "the liver progenitor cells are less than 15 microns. Any separation method that separates *such* small cells from *larger* cells . . . is suitable," page 26, line 30. Emphasis added. As another example, the specification states that

"[l]arge cells, including mature parenchymal cells and tetraploid cells, are sedimented faster than the small progenitor and diploid cells, and are removed." Page 27, line 12. Reconsideration of the rejection is requested.

The Examiner rejects claims 1, 10, 21, and 42 for use of the phrase "one or more markers indicative of expression of alpha-fetoprotein, albumin or both" as vague and unclear. The objected-to phrase is clearly defined in the specification on page 27 line 28 *et seq.*

The Examiner objects to the term "less than about 15 microns" in claim 3 as being vague and rendering the claim indefinite. The size of the cells is extensively disclosed in the application. For example, the specification teaches that "[t]he isolated progenitors can be diploid and can be less than about 15 microns in diameter." Page 12, line 18. As another example, the specification states that "[l]arge cells, including mature parenchymal cells and tetraploid cells, are sedimented faster than the small progenitor and diploid cells, and are removed." Page 27, line 12. Applicants maintain that the teaching is abundantly clear to one of skill in the art. Reconsideration of the objection is respectively requested.

The Examiner objected to claim 12 on the basis of lack of a step to link step (a) and step (b) with the preamble.

The MPEP states that:

> [A] preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or . . . where the body of the claim does not depend on the preamble for completeness, but, instead, the process steps or structural limitations are able to stand alone.

MPEP 2111.02.

In claim 12 the process steps can stand alone. The preamble phrase "of providing a composition comprising an enriched population of human liver progenitors" can be viewed as merely reciting a purpose of the claimed process.

The Examiner alleges that the phrase "an adult liver cell-specific marker" is vague and renders claim 17 indefinite. Applicant respectfully draws the Examiner's attention to the specification, where the phrase "an adult liver cell-specific marker" is clearly and unambiguously defined on page 29 line 27 *et seq.*

The Examiner requested clarification of claim 21 to remove indefiniteness. Claim 21 has been amended to delete the words "human liver" after the word "which" to clarify the invention.

The Examiner objects to claim 35 for the lack of a link between the steps and the preamble. Applicant asserts that claim 35 is patentable without a specific link for the reasons enunciated in the argument to claim 12, above. In particular, the preamble phrase "of treating a disease in a subject in need thereof" merely recites a purpose of the claimed method. MPEP 2111.02.

No new matter has been added.

Rejections Under 35 U.S.C. §102(b).

Claims 1-8, 10-16, and 18-20 were rejected as being allegedly anticipated by Muench *et al.* Blood 83:3170, 1994 or Muench *et al.* Blood 89:1364, 1997. Applicants respectfully traverse the rejection.

Applicants have amended claims 1 in the instant application to reflect the incorporation of additional step (c) directed to the selection of cells, which themselves, their progeny, or more mature forms thereof exhibit one or more markers indicative of expression of alpha-fetoprotein, albumin, or both, and which additional step was first recited in prior claim 10, now canceled. Applicants respectfully assert that amended claim 1, and hence, all the claims which depend therefrom, are novel over the disclosure of the references cited by the Examiner. In particular, none of the cited references disclose the subject matter of step (c). Reconsideration of the rejection is respectfully requested.

With regard to claim 12, Applicants have amended claim 12 to recite that the immunoselection step is one which provides "a mixture of cells . . . which mixture of cells is comprised of an enriched population of human liver progenitors, which human liver progenitors themselves, their progeny, or more mature forms thereof exhibit one or more markers indicative of expression of alpha-fetoprotein, albumin, or both." Applicant respectfully asserts that amended claim 12 and, hence, all the claims which depend therefrom, are novel over the disclosure of the references cited by the Examiner. In particular, none of the cited references

disclose a method which provides for the mixture now recited in the amended claim. Reconsideration of the rejection is respectfully requested.

Claims 21-23 and 42-44 were rejected as anticipated by the Muench *et al.* references.

Applicants assert that Muench et al., 1994 and 1997, do not disclose the subject matter of claim 21, specifically an enriched population which exhibit one or more markers indicative of expression of alpha-fetoprotein, albumin, or both. Reconsideration of the rejection of claim 21 and claims 22 and 23, which depend from claim 21, is respectfully requested.

Applicants assert that Muench et al., 1994 and 1997, do not disclose the subject matter of claims 42-44. Muench et al. do not assess the expression of either alpha-fetoprotein or albumin or the correlation of expression of either protein with any marker described in Muench et al. Moreover, Applicants assert that there is no indication that the cells that Muench et al. identify inherently express either alpha-fetoprotein or albumin. "The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic." MPEP 2112. Reconsideration of the rejection of claims 42-44 is requested.

Claims 1-16, 18-23, and 42-44 were rejected as anticipated by Craig *et al.*, J. Exp. Med. 177: 1331, 1993.

For the reasons discussed above, Applicants respectfully maintain that the cited reference does not disclose the elements of the invention as claimed in rejected claims 1-16, 21-23 and 42-44. Reconsideration of the rejection is requested.

Rejection under 35 U.S.C. §102(e).

Claims 11, 20, 21-26, and 42-44 were rejected as allegedly anticipated by Faris (US Patent No. 6,129,911).

For the reasons discussed above, Applicants respectfully maintain that the cited reference does not disclose the elements of the invention as claimed in the amended claims. Reconsideration of the rejection is respectfully requested.

Rejections Under 35 U.S.C. §103.

Claims 1-6, 8, 10, and 12-19 were rejected as unpatentable over Reid *et al.*, U.S. Patent No. 6,069,005. Further, claims 21 and 38 were rejected as obvious over Muench (1994 or 1997) in view of Reid (US Patent No. 5,789,246). These rejections are respectfully traversed.

For the reasons discussed above, Applicants assert that the cited references do not teach or suggest the subject matter of the amended claims. Further, Applicants respectfully maintain that the subject matter of the amended claims are not disclosed in the cited references, nor obvious from the references, in that the secondary references do not remedy the deficiencies of the primary references. Hence, no prima facie case of obviousness has been established even assuming that the cited references have been properly combined.

CONCLUSION

Applicants believe that all stated reasons for rejection and objection have been overcome. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections, and that they be withdrawn.

If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned directly.

AUTHORIZATION

A Petition for a two-month extension of time, and fee, were filed on even date herewith. No additional fees are believed to be necessary. However, the Commissioner is hereby authorized to charge any fees, including the fees for the net addition of claims, which may be required for this Response, or credit any overpayment to Deposit Account No. 50-0436. In the event that an Extension of Time is required, or which may be required in addition to that requested in a petition for an Extension of Time, the Commissioner is requested to grant a petition for that Extension of Time which is required to make this response timely and is hereby authorized to charge any fee for such an Extension of Time or credit any overpayment for such an Extension of Time to Deposit Account No. 50-0436.

Respectfully submitted,

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